FDA Executive Summary

Prepared for the
April 12, 2016 meeting of the
FDA's Pediatric Advisory Committee

H020007

Medtronic Activa Neurostimulator for Dystonia Treatment

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-market experience with the use of the Medtronic Activa® Dystonia Therapy in pediatric patients since approval in 2003. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-market safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the HDE remains appropriately approved for pediatric use.

The Medtronic Activa® Dystonia Therapy system is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.

This memorandum summarizes the safety data regarding H020007 through the present day including pre-market clinical data, post-market medical device reporting (MDR) for adverse events, and peer-reviewed literature regarding safety data associated with the device.

II. ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA

1. The Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C) and allowed HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN was defined to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States." FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. The number of devices implanted in the U.S. in CY 2015: 887 implants; the number of active implants in the U.S. during CY 2015: 3365 active implants; number of devices implanted in pediatric patients in the U.S. in CY 2014 (<22 years): 159 implants; number of active implants in the U.S. for pediatric patients (<22 years) during CY 2015: 601 active pediatric implants.

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting, including
  - rare, serious, or unexpected adverse events
  - adverse events that occur during long-term device use
  - adverse events associated with vulnerable populations
  - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

<u>MDRs Associated with the Medtronic Activa Neurostimulator for Dystonia Treatment</u>

The Agency searched the MDR database to identify reports associated with the Medtronic Activa Neurostimulator for Dystonia Treatment entered September 28, 2014 – September 27, 2015. The searches resulted in the identification of 333 unique MDR reports. For the purposes of this MDR analysis, these 333 MDRs will be referred to as the 2016 Pediatric Advisory Committee (PAC) data. Two of the reports were submitted by voluntary reporters, one by a user facility, and the

remaining 330 MDRs were submitted by the manufacturer. Patient gender information was reported in 307 of the MDRs in which 162 were female and 145 were male patients. The event types by age category are presented in Table 1.

Table 1. Event types by age category for MDRs included in the 2014, 2015 and 2016 PAC data sets.

	PAC 2014			PAC 2015			PAC 2016		
Event Type	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**
Malfunction	14	46	11	19	91	26	22	101	22
Injury	35	101	65	22	84	38	34	122	29
Death	0	2	0	1	1	0	0	0	3
Total	49	149	76	42	176	64	56	223	54

The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2016 PAC data is presented by age category in Table 2. The majority of MDRs originated from within the US.

Table 2. The Number of US and OUS MDRs by Age Category

Reporter Country	Pediatric	Unknown	Adult	Total
US	48	17	198	263
OUS	25	6	36	67
Unknown	2	1	0	3
Total	56	54	223	333

Tables 3 and 4 show the most frequently reported device and patient problem codes as provided in the pediatric MDRs. These codes are useful in obtaining a general overview of what is being seen in the MDRs; however, they do not provide the full picture of the events occurring. The most frequently reported patient and device problem codes in the adult and unknown age populations were similar to those reported in the pediatric MDRs. For purposes of comparison, the most frequently reported pediatric patient and device problem codes are presented with the corresponding adult and unknown age numbers for each code in Tables 3 and 4.

Table 3. The most frequently reported pediatric patient problem codes and the corresponding numbers for the adult and unknown age population for each code for the 2016 PAC

Patient Problem Code	Pediatric	Unknown	Adult
Therapeutic Response, Decreased	16	7	39
No known impact or consequence to patient	13	14	67
Complaint, Ill-Defined	12	10	44
Infection	12	12	27

Neurological Deficit/Dysfunction	11	8	34
Therapeutic Effects, Unexpected	8	10	43

*The problem code counts for the adult and unknown age categories are presented for comparative purposes.
**A single MDR may be associated with more than one problem code. Therefore, the total number of problem codes may not equal the total number of MDRs.

While the exact numbers fluctuate from year to year, the reported patient problem codes were similar between the 2015 and 2016 PAC data sets and no new patient problems were identified based on the patient problem codes. It should be noted that infection was reported more frequently within the 2016 pediatric PAC data (N=12) compared to the 2015 pediatric PAC data (N=1). The 2016 number is similar to what was presented at the 2014 PAC. Additionally, a similar increase in infection reports was seen in the adult population between 2015 and 2016.

Table 4. The most frequently reported Device problem codes for the 2016 PAC

Device Problem Code	Pediatric	Unknown	Adult
Impedance Issue	21	25	43
No Known Device Problem	15	12	51
Device operates differently than expected	14	13	49
Battery/Charging Issue	10	10	48
Failure to deliver energy	8	3	26
Device displays error message	7	2	20
Intermittent continuity	5	2	6

*The problem code counts for the adult and unknown age categories are presented for comparative purposes.
**A single MDR may be associated with more than one problem code. Therefore, the total number of problem codes may not equal the total number of MDRs.

The reported device problem codes were similar between the adult and pediatric population, and between the 2014, 2015 and 2016 PAC data sets. Frequently reported device problems in the 2016 PAC data included impedance issues (including low, high, and general impedance issues), no known device problem, the device operating differently than expected (a catch-all code that is used for a variety of issues, mostly related to a change in stimulation effect for the patient.), battery/charging issues and failure to deliver energy. No new device issues were identified based on the reported device problem codes.

Pediatric MDR Review

Patient age was able to be determined in 279 of the MDRs, which included 56 pediatric reports and 223 adult reports. The patient age was unknown in 54 reports. Pediatric patient age ranged from 2 to 21 years of age. The average age of the pediatric patients was 15.7 years. The reporting country was available in 54 of the 56 pediatric MDRs and included the United States (N=48), Japan (N=3), China (N=2) and Germany (N=1). There were 21 female and 35 male pediatric reports.

Time to Event (TTE) for Pediatric MDRs

In an effort to separate reports for events that occurred zero to 30 days post implant from those that occurred greater than 30 days post implant, an analysis of the time to event (TTE) was conducted on the pediatric MDRs. The TTE was calculated based on implant date provided, date of event provided, and the event text for each report. The TTE was only able to be conclusively determined for 23 of the pediatric reports received. Reported problems and event types for pediatric MDRs by TTE are presented in Tables 5 and 6. There were eight reports in which the event occurred between zero and 30 days post implant procedure and 15 reports in which the event occurred more than 30 days post implant procedure.

Table 5. Reported problems and event types for pediatric MDRs by TTE ≤ 30 days

Reported Problem	Injury	Malfunction
Device explanted due to infection	2	0
Device replaced due to battery failure	1	0
Patient stroke during implant procedure	1	0
Device replaced due to impedance issues of unknown cause	1	0
Device replaced due to intraoperative lead fracture	0	2
Impedance issue of unknown cause	0	1
Total	5	3

Table 6. Reported problems and event types for pediatric MDRs by TTE > 30 days

Reported Problem	Injury	Malfunction
Return of symptoms due to parameter changes from a potential EMI of unknown cause	2	0
Device replaced due to mood changes and loss of therapeutic effect	2	0
Return of symptoms due to unknown cause	2	0
Device replaced due to impedance issues related to a patient fall	2	0
Device explanted due to infection	1	0
Device replaced due to normal battery depletion	0	2
Intraoperative impedance issue	0	1
Intermittent shutoff due to unknown cause	0	1
Intermittent shutoff due to potential EMI of unknown cause	0	1
Impedance issue of unknown cause	0	1
Total	9	6

All pediatric reports were individually reviewed to identify events that were previously determined to be clinically significant or concerning by CDRH clinicians, and to be consistent

with the prior MDR analyses. The specific adverse events are presented in Table 7 and explained in detail in the appropriate subsections below. Please note that more than one contributing factor may have been associated with each of the events presented in Table 7 and described below in detail.

Table 7. Clinically concerning pediatric reports

Adverse Event	Count
Device explanted	32
Device replaced	24
Return or worsening of symptoms	24
Infection	10
Battery/charging issue	9
Growth related issue	6
EMI	6
Lead break/fracture	5
Stroke	3
Cognitive issue	3

* A single MDR may be associated with more than one type of adverse event.

- *Device Explant (N=32 MDRs, 21 unique events) and Device Replacement (N=24 MDRs, 16 unique events)*: All MDRs associated with device replacement also reported device explant. Further, device explant and replacement were associated with similar clinical issues. In the 24 MDRs that reported both device explant and replacement, the contributing factors included impedance issues (N=12), lead fracture (N=5), infection (N=3), encapsulation of device into bone/connective tissue (N=2), normal battery depletion (N=2), neurological deficit (N=2), behavioral changes (N=2), patient growth (N=1) and battery failure (N=1).

  Additionally, there were eight MDRs (associated with five unique events) in which the device was explanted and not replaced. These reports were associated with infection (N=6) and "mild stroke after implant" (N=2). Please refer to the sub-sections on infection and stroke for additional information on these reports.

- *Worsening or Return of Dystonia Symptoms (N=24 MDRs, 16 unique events):* Worsening or return of dystonia symptoms was associated with several different device problems. The reported problems that contributed to worsening or return of symptoms were battery/charging issues (N=5), impedance issues of unknown cause (N=5), unknown causes (N=4), lead breaks (N=3), device reset due to potential EMI (N=2), impedance issues potentially due to patient growth (N=2), lead enclosed in bone or connective tissue (N=2) and intermittent device shut off (N=1). The majority of these issues were resolved, although device replacement was required in some cases (N=10).

- *Infection (N= 10 MDRs, 7 unique events):* Limited information was provided on the potential causes of the infections reported in the MDRs. In some of the infection reports organisms associated with the infection were provided. These organisms included "fungus" (N=2 *Staphylococcus aureus* (N=4), Group A Streptococcus (N=1) and unknown (N=3). The infections were treated with antibiotics (oral and intravenous), debridement and device explant. One MDR reported that a patient may have experienced cognitive changes due to infection. The MDR did not indicate if the cognitive changes were transient or not, and no information on the patient outcome was provided.

- *Battery/Charging issue (N= 9 MDRs, 7 unique events):* The majority of the battery/charging issues were associated with difficulty recharging due to coupling problems (N=2), issues with recharging remote (N=3) and a "flipped implantable neuro stimulator (INS)" (N=1). Intermittent continuity (N=1) and premature battery depletion (N=4) were also reported. These battery/charging related issues resulted in return of patient symptoms (N=5), pocket revision (N=1), loss of therapy (N=1), device replaced (N=1), and no known impact on patient (N=1).

- *Patient Growth Related Issues (N=6 MDRs, 4 unique events):* Potential growth-related issues were reported in six MDRs (four unique events associated with two patients) and were associated with rapid patient growth resulting in "mechanical issues" (N=2), multiple system revisions due to patient growth (N=2) and possible "tension on extension" due to growth (N=2). The ages of the patients associated with these reports ranged between 16 and 17 years old.

- *Electromagnetic Interference (EMI) (N=6 MDRs, 3 unique events):* There were six pediatric MDRs (three unique events) associated with potential EMI. Sources of EMI included exposure to a "standing X-ray" (N=2) and unknown sources (N=4). Based on the limited information provided in the MDRs, the impact of EMI on the device is unclear, but may be associated with inadvertently changing device settings or turning off the device.

- *Lead break/fracture (N=5 MDRs, 4 unique events):* There were five MDRs associated with lead break/fracture. All of these MDRs resulted in device replacement. The types of lead breaks included intraoperative lead fracture (N=2), and electrode fracture with unknown cause (N=1). Additionally, in one event (associated with two MDRs) the conductor on the proximal end of the lead was broken due to possible patient growth (N=2).

- *Stroke (N=3 MDRs, 2 unique events):* In one event a 15 year old patient experienced a "mild stroke after implant". No patient outcome was reported. In the second event, a ten year old patient experienced a left brain stroke at the time of implant, which resulted in limited ability to move their right arm and leg, as well as inability to speak. After significant rehabilitation, the patient was able to speak in a "faint" voice, and was able to walk, although not for long distances. The patient was receiving therapeutic effect from the device and was doing better than her baseline prior to the device implant, despite the

stroke. No information regarding potential contributing factors to the reported strokes was provided in the MDRs.

- *Cognitive issues (N=3 MDRs, 2 unique events):* In one event it was reported that a patient had altered mental status, potentially due to device related infection. In the second event, it was reported that the patient was experiencing mood changes due to Globus Pallidus (GP) stimulation. The patient's school teachers noticed a "significant change in the patient's behavior". The patient turned off the device which resolved the mood changes, but resulted in diplopia. The device was explanted and replaced which resolved the mood changes and diplopia.

MDR Conclusions

A total of 56 MDRs reporting 39 unique events were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. A return or worsening of dystonia symptoms (loss of therapeutic effect) was the most frequently reported pediatric patient problem. This type of patient problem is often indicative of an issue that can be resolved. The labeling does address the issue of symptom return/worsening and these events are known to occur with the use of other neurostimulators. Other reported patient problems, including infection, are noted in either the device labeling or clinical summary.

The most frequently reported device problem was impedance issues. The device labeling states that issues with open circuits (high impedance) can occur without warning and impedance issues are also known to occur in other neurostimulators. Other device problems that occurred within the MDRs are either noted in the device labeling or are known device issues with neurostimulator devices in general. No new device or patient problems were identified in the 2016 PAC data when it was compared to the 2014 and 2015 PAC data.

IV. POSTMARKET DATA: LITERATURE REVIEW WITH FOCUS ON SAFETY DATA

Purpose

The intent of this systematic literature review is to provide an update of adverse events associated with the use of the Medtronic Activa neurostimulator since the previous literature review for the 2015 PAC meeting. Specifically, the systematic review was conducted to address the following question: What is the safety of Medtronic Activa neurostimulator devices in the pediatric population treated for dystonia?

Methods

The review team agreed on the following search string for conducting the search: (medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic

activa) OR activa OR (dbs AND pediatric AND Dystonia). PubMed and EMBASE databases were systematically searched on November 5th, 2015. Papers published since the last search, i.e. during the period November 11, 2014 to November 5, 2015 (both dates inclusive) were included. Then, the following exclusion criteria were applied, either from reading of the abstracts or the full article:

1. Conference abstracts
2. Duplicates
3. No primary dystonia
4. Non-pediatric population or mixed (pediatric and adult) population where pediatric and adult subjects are not analyzed separately
5. No humans in the study (i.e. animal study)
6. Not written in English
7. Unavailable article
8. Unrelated topic
9. No Medtronic software used

The adverse events reported in the publications were described.

Results

The search string yielded a total of 46 publications. Of these, four were duplicate publications between the EMBASE and PubMed databases.[1-4] Amongst the 42 publications we reviewed, 41 publications fulfilled the exclusion criteria as listed in figure 1.[1-41] This included three publications that reported outcomes in secondary dystonia and not primary dystonia i.e. off-label use of the neurostimulator.[2,40,41] One of these three publications reported adverse events related to infection.[2]

One article was retained for final review: *Rizzi et al*[42].

1. *Rizzi et al* studied the implantation costs of nonrechargeable internal pulse generator (IPG) versus the estimated costs of rechargeable IPGs.[42] In this study, group 1 included 11 patients with dystonia and age <22 years, our population of interest. The mean age was 13.5 years (range 8-21 years). These patients were implanted with double channel IPG (N=1) or single channel IPG (N=10). Patients were followed for a mean period of 7.6 years (standard deviation ± 3.9 years). No unilateral DBS was performed in this group. Mortality rate, from causes other than DBS, was 9.1%. The total number of IPG replacements was 22 and time-to-replacement had a mean of 3.2 years (range 2 – 5 years). Total number of adverse events after DBS, and before the first replacement, was zero. Total complications after IPG replacement was 27.2%. 18% of the complications were ascribable to IPG replacement (2 single channel IPGs). Individual complications were not listed, however. [42]

Summary

From our previous literature review, we had concluded that DBS is a safe alternative for dystonia in pediatric population refractory to standard of care therapies. It, however, requires implantation of a device into the brain, and therefore the device is not without risk. Our systematic review had revealed that in terms of safety, the common adverse events were infection, incorrect stimulation parameters leading to normal and expected transient side effects, partial seizures in a case of lead movement to temporal lobes, transient events like anxiety, dyskinesia, and depression, motor and sensory symptoms from the direct effect of stimulation, and ineffectiveness.

This time, the databases were searched for the period November 11, 2014 to November 5, 2015, and forty two non-duplicated articles were found. After applying the exclusion criteria, only one publication was retained for the final review. Similar to the systematic review presented in the previous PAC meetings, this review did not reveal a novel safety event. The publication did not list the adverse events. These findings are consistent with our conclusions from the systematic review conducted for the previous PAC meeting.

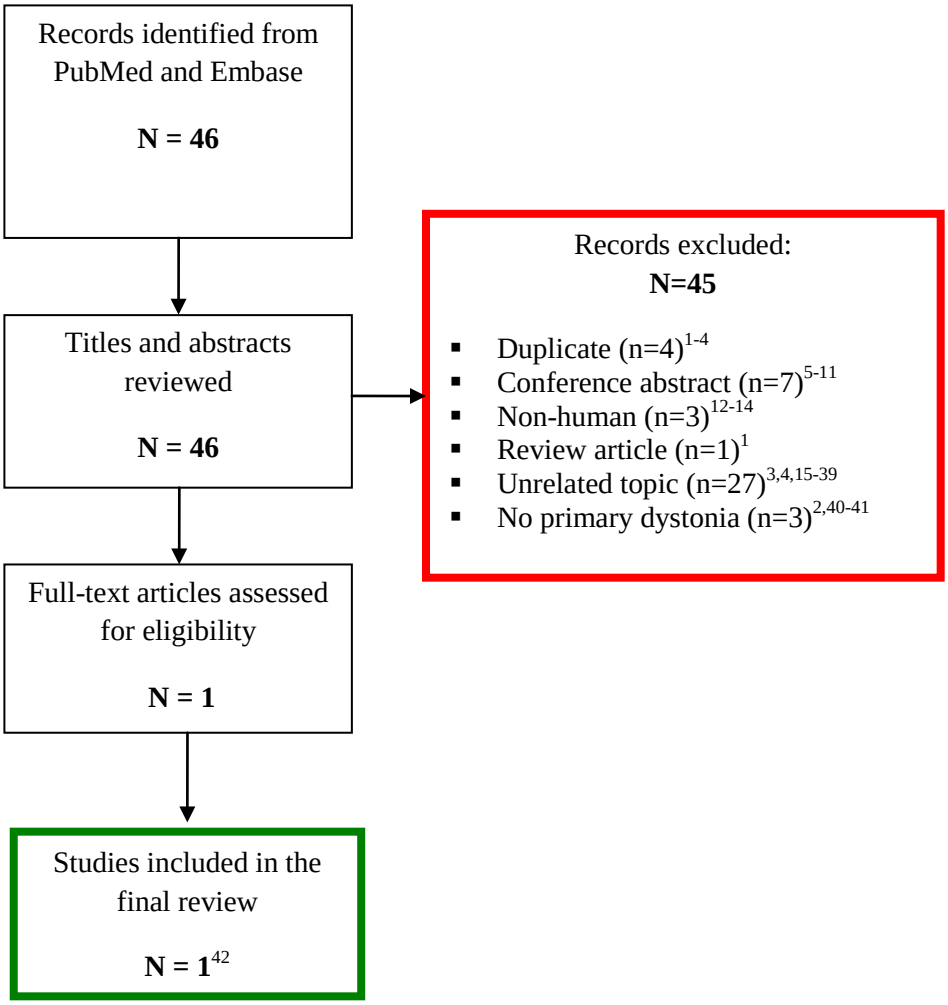

Figure 1: Work flow for the systematic literature review (Period: November 11, 2014 to November 5, 2015)

SUMMARY

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003. Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use. FDA will continue routine surveillance including MDR and literature reviews. FDA will provide focused updated safety and use data to the PAC in 2017.

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